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10/572,750	03/21/2006	Taku Demura	P29533	3329

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
07/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/572,750	DEMURA ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2009 and 26 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *5,6,8-10 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,11-15 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of "target sequence bound to the adaptor sequence" and "phosphorylation of the 5' end of either or both ends of a cassette construct" in the reply filed on 4/26/2010 is acknowledged. Applicant states Claims 1-3, 7, 11-15, and 17-20 read on the elected species. It is noted that the embodiment "target sequence bound to the adaptor sequence" embraces and does not exclude the embodiments defined by claims 14 and 15. See also the "or both" limitation in the final line of claim 1. Accordingly, the restriction between these embodiments, recited in the alternative in the final two lines of claim 1, is withdrawn.

An earlier action acknowledged Applicant's election with traverse of Group I, claim(s) 1-4, 7, 11-15, 17-20, drawn to a cassette construct for preparing an inverted repeat sequence, and to plasmid, expression vectors, and host cells thereof. See Applicant's reply filed 4/22/2009.

Status of Application/Amendment/Claims

Applicant's response filed 12/10/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/10/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

With entry of the amendment filed on 12/10/2009, claims 1-3 and 5-20 are pending.

Claims 5, 6, 8-10, and 16 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 7, 11-15, and 17-20 are examined herein.

Information Disclosure Statement

The signed and dated IDS filed 6/12/2006 is included herewith, with the additional annotation providing the publication year of the Lee et al. reference, missing from the originally filed IDS.

Specification/Sequence Compliance

The objection to the disclosure because of missing sequence identifiers is withdrawn in view of the amendment to the specification filed 2/21/2007. The amendment has been entered into the application.

Claim Objections

Claims 3 and 13 are objected to because of the recitation "phosphorylation of the 5' end of either or both ends of a cassette construct." The use of the indefinite article "a" renders the limitation as a whole ambiguous, because it does not clearly refer to the cassette construct that is claimed. It may be taken as a limitation referring to any cassette construct. For clarity, it is requested applicant use "the" or "said" to specify which construct is being referenced in the limitation. Similar issues arise in the non-elected species of each claim, added by amendment on 12/10/2009.

It is further noted that the limitation "either or both ends of the cassette construct" in lines 1-2 of claims 3 and 13 lacks explicit antecedent basis in the claims.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 13, 15, 17, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 and 13 each recite the limitation "the 5' end." There is insufficient antecedent basis for this limitation in the claims. For that matter, there is insufficient antecedent basis for "either or both ends of the cassette."

Claim 3 and claims depending thereon are further indefinite because of the recitation "prior to target sequence binding." The claims do not specify and no clear implicit meaning can be ascertained for "binding." One can only assume the term "binding" is referring to, perhaps, ligation or other covalent linkage. The term "binding" in the nucleic acid art, however, takes on many meanings, including hybridization as well as other non-covalent interactions with both nucleic acids, proteins, and small molecules. The limitation "target sequence binding" could mean any of these. The claims do not identify the other element to which binding is occurring. As a result one of skill would not reasonably be apprised as to what does or does not infringe the claims.

Claim Rejections - 35 USC § 112, first paragraph (new matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 11-15, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Adequate written description support is not found in the instant application for the genus of cassette constructs, wherein "a target sequence" is bound "to the adaptor sequence and the inverted sequence of the adaptor sequence." As shown in Fig. 1, it is not possible in Applicant's invention for "a target sequence" (singular) to be bound or directly coupled to both the adaptor sequence and the inverted adaptor sequence as implied by claims 1, 14, and 15. Instead, what is shown by the disclosure is a construct in which head to head inverted repeats of the target gene flank a sequence consisting of, in order, in the 5' to 3' direction, an adaptor sequence, a spacer sequence, and inverted adaptor sequence. There is no explicit or implicit disclosure or representation of a construct in which a single target sequence is simultaneously bound directly to an adaptor and inverted adaptor, as now embraced by the claims.

Additionally, adequate written description support is not found for the expression vector defined by claim 11 comprising an "amplification product." While the specification discusses PCR amplification of a construct once constructed (paragraphs 57 *et seq.*), there is no disclosure readily identifiable from either the paragraphs cited by applicant in the remarks filed 12/10/2009 or anywhere else in the application describing the preparation of a construct by subcloning into a vector or other cassette a single amplified product containing each of the elements listed in claim 11.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended

claims, applicant should show support in the original disclosure for the new or amended claims. The purpose of the written description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." MPEP 2138.05, I.

In the instant case, in the remarks filed 12/10/2009, Applicant points to paragraphs 49-56 of the published application. However, a review of these cited passages, and, indeed the entire application, fails to find explicit, implicit, or inherent description by words, structures, figures, diagrams, or formulas of the specific limitations now recited in the claims (summarized above) in a manner that would convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the genus of siRNAs having each of these features, as now claimed. See MPEP 2163.

Accordingly, the instant claims as a whole are rejected for lack of written description support because one of skill would not recognize applicant was in possession of the product siRNAs now claimed at the time of filing. Dependent claims are rejected therefor. Should Applicant disagree with the finding, Applicant is invited to point out with particularity where and how written description support may be found in the original application.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Sui et al. (2002) " A DNA vector-based RNAi technology to suppress gene expression in mammalian cells" *Proc. Natl. Acad. Sci* 99:5515-5520 is withdrawn in view of Applicant's amendment to

claim 1 and in view of the special meanings of the terms "adaptor" and "spacer" provided by the specification at page 6.

MPEP 2111.01.IV states where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999).

In claim 1, the meanings of the terms "adaptor sequence" and "spacer sequence" are interpreted according to the definition provided by the specification at page 6 (as filed on 3/21/20006) , where it is stated that:

1. A spacer sequence must be a nucleotide sequence that is not related to a target sequence or an adaptor sequence (i.e., a sequence that does not complementarily bind to a target sequence or an adaptor sequence *in vitro* or *in vivo).*

2. An adaptor sequence and an inverted adaptor sequence are each independently a nucleotide sequence that is not related to the nucleotide sequence of a target sequence, a spacer sequence, or a plasmid vector used (i.e., a sequence that does not complementarily bind to a target sequence, a spacer sequence, or a plasmid vector used *in vitro* or *in vivo).*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 7, 11, 12, 15, 17, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Brummell et al. (2003) "Inverted repeat of a heterologous 3'-untranslated region for high-efficiency, high-throughput gene silencing" *The Plant Journal* 33:793-800.

Claim interpretation:

Applicant will note that, apart from claim 20, none of the claims impose any particular order or require any particular positions of the adaptor, inverted adaptor, spacer, target sequences relative to one another. While claim 1 now requires that the target sequence is bound to the adaptor, the spacer and inverted adaptor sequences could be located anywhere in the construct while still satisfying the claim. Furthermore, the claim does not require direct linkage to the adaptor, but embraces indirect linkage, as through a restriction site or other sequences. This interpretation is supported by at least claims 14 and 15, wherein applicant claims "a" target sequence bound to both an adaptor and an inverted adaptor. The only conceivable manner in which this could occur is if intervening sequences are allowed to link the target gene to each element.

Further, the claims do not exclude plural target genes, spacers, or adaptors. Additionally, there is no minimum or maximum length requirements of any of the elements. A single nucleotide could be a spacer, for example. Two or more nucleotides in the proper relative sequences could qualify as adaptor and inverted adaptor sequences. A palindromic restriction site could qualify as a spacer or an adaptor. To be sure, a single palindromic restriction site could be said to include both an adaptor sequence and an inverted adaptor sequence; the claims are not limited to single or double stranded sequences, but embrace all possible constructs, both single and double stranded. However, as evidenced by at least Claims 3 and 13, the claims clearly

embrace double stranded constructs, since the claims imply it is possible to phosphorylate two 5' ends, which could only happen if the construct was double stranded. Therefore, the inverted sequence referred to in the claims could be in the same strand or the opposite strand. It's unclear. In fact, at present, the true scope of what applicant has actually invented can only be precisely identified by comparing the claim language to the figures. However, it would be improper to import limitations from the figures into the claims. As a whole, the claims are extremely broad. While the definitions for adaptor and spacer sequences at page 6 of the specification (cited in relevant part above) govern the interpretation of the claims, these definitions alone fail to distinguish the many elements present in the many different inverted repeat constructs disclosed in the prior art, including that of Brummel et al.

Claims 3 and 13, describing a pretreatment, are interpreted as products-by-process, according to the guidelines in MPEP 2113. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art. The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. *In re Fessmann,* 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product

appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

In the instant case, while claims 3 and 13 require 5' phosphorylation prior to target sequence binding, the claims do not clearly require the presence of a 5'-phosphate at one or both ends of the final construct as claimed. The pretreatment appears to disclose features present in an intermediate, but does not explicitly requires such features be present in the final product, and there is no evidence showing the presence of 5' phosphates in the intermediate would materially alter the structure of the final product. Accordingly, it is difficult to distinguish the construct defined by claim 3 and 13 from that described by Brummel et al. Even if the claim were to require the presence of 5' phosphates, one of skill would reasonably conclude any such construct would have similar if not identical properties and be equally suited for cloning and expression purposes.

With regard to claim 11, whether a sequence has or has not been amplified does not alter the structure of the sequence. The claims remain drawn to products, not methods of making said products. The patentability of the products is based on what they are, not what they do or how they are made, unless the manufacturing process steps impart distinctive structural characteristics to the final product.

With regard to claim 20, the claim requires nothing more than 1) an adaptor sequence, 2) a spacer sequence, and 3) an inverted sequence of the adaptor sequence, wherein the spacer sequence is between the adaptor sequences. Brummel et al. clearly shows a construct meeting

these limitations. The *nos* gene could be seen as an adaptor and inverted adaptor: it is unrelated to a target gene, such as the *PG* gene ,and the spacer. Alternatively, any of the restriction sites could be seen, independently, as spacers or adaptors. The claim embraces both direct and indirect connections between the elements: there is no requirement that any of the elements are immediately adjacent to one another. The limitation "between" is satisfied even if there are several other intervening elements. The claim does not exclude multiple spacers, adaptors, or target genes and embraces all possible lengths of such elements and any number of contiguous and non-contiguous relationships therebetween.

Brummel et al. taught an inverted repeat expression construct (Fig. 1, page 794) comprising an FMV promoter, a hsp70 leader sequence, a PG transgene (target sequence) linked to a *nos* sequence (adaptor) through a PstI site (adaptor and inverted adaptor), and a spacer sequence flanked by inverted repeats of the 3'-untranslated region of the *nos* gene (adaptor and inverted adaptor). The inverted repeats of the nos gene are further separated by BamHI and BglII sites, which each could also be considered to be spacers, adaptors, and/or inverted adaptors. The construct further includes an NcoI site separating the PG transgene from the promoter. At page 798, left column, it is taught the construct was cloned into a SVS297 plasmid for transformation of plant cells. Accordingly, one of skill would instantly have envisioned the construct, the vector, and the host cells transformed by said vector.

With regard to claim 11, Brummel et al. teaches the portion of the *PG* gene used in the construct was amplified (page 797 bridging to 798).

Indeed, the construct of Brummel et al. anticipates the generically defined and broadly claimed construct in multiple manners, depending on which elements therein one considers to represent the spacer, adaptor, inverted adaptor, and target sequences.

***

Claims 1-3, 7, 11-15, and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (2003) *Methods* 30:322-329.

The claims are interpreted as above.

With regard to claims 1, 3, 7, 11, 12, 15, 17, 19, and 20, Lee et al. disclosed an inverted repeat expression construct comprising a UAS promoter, head to head inverted repeats of a target gene sequence separated by an *Sfi* I site having the sequence GGCCATCTAGGCC (i.e., an adaptor, spacer, inverted adaptor sequence). See Fig. 1 and accompanying text describing the construct at page 323). The target sequence is bound to the adaptor sequence and, via intervening sequences, to the inverted adaptor. From the discussion in Lee et al., it is clear the construct is intended for inclusion in appropriate expression vectors and transformation of cells. Therefore, one of skill would immediately have recognized the plasmids, vectors, and host cells comprising the construct shown in Fig. 1. Whether the individual elements were cloned or ligated into the construct separately or prepared as a single amplification product would not have altered the structure or nature of the construct and all such constructs would be structurally indistinguishable.

With regard to claim 3 and the like, the claims do not require the presence of a 5' phosphate, but merely pre-phosphorylation of an empty cassette prior to target sequence binding. While Lee et al. do not teach pretreatment of this type, it is unclear whether the final construct

described by Lee et al. differs from the final product defined by claim 3 (i.e., whether the pretreatment results in a structurally distinct product). Moreover, even if the claimed construct differs from that disclosed by Lee et al., the presence or absence of a 5' phosphate at one or both ends would reasonably be considered to be functionally indistinct from that described by Lee et al. The cassette would be prepared in a manner consistent with its ultimate use, which includes placement in a suitable and operable expression vector. One of skill in the molecular biological arts would introduce or remove phosphates as required to enable ligation into the vector or recombination with the host genome, as the case may be.

With regard to claim 2 and claims depending thereon, Lee et al. also disclosed a construct for generating an inverted repeat of essentially any desired target gene, comprising tail to tail repeats of a target gene separated by a *Pst* I site, a 5' splice site, and an intron, such as the *white* intron. Other variations of the construct, including a plasmid cloning and expression vector comprising intron spacers and palindromic restrictions separating the inverted target sequence repeats are also disclosed (see Figs. 2, 4, and 5, and accompanying text). The preparation of the construct may involve an amplification step.

Accordingly, the constructs disclosed by Lee et al. are indistinguishable from those now claimed.

Response to Arguments

Applicant's arguments filed 12/10/2009 have been fully considered as they may bear on the new and reiterated rejections above.

In traversing the rejection over Brummell et al., Applicant argues Brummell et al. does not require an inverted repeat DNA of the target gene. Applicant argues a limitation not found in the claims. The claims do not require an inverted repeat of the target gene. Moreover, Brummel et al. does in fact disclose a construct having an inverted repeat of a target gene, the *nos* gene. Even if the nos gene is not the intended silencing target, it share homology/ complementarity with a gene in a plant and therefore is a "target" under that definition. Moreover, the claims do not discriminate between chromosomal gene sequences and mRNA sequences. Thus the term "target" includes any gene sequence, DNA or RNA. The limitation "target sequence in RNA interference" does not clearly limit the claims to a processed mRNA, since mRNA sequences are found in the genome and are still reasonably considered "target" sequences. Further, mRNAs can comprise 3' UTRs, are targetable by RNAi mechanisms.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
July 12, 2010